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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,540	06/21/2001	Robert Klein	R-193/40338.119USU1	5814

26619 7590 11/02/2004

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/887,540	KLEIN, ROBERT	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,13-19 and 24* is/are pending in the application.

4a) Of the above claim(s) *1-4 and 13-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-19 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application contains claims 1-4 and 13-16 drawn to an invention nonelected with traverse in Paper No. 10. Applicants mistakenly list claims 1-5 and 13-16 as withdrawn (see claims from 2-27-04). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 5-12, 20-23 and 25 remain cancelled. Applicants mistakenly list only claims 5-12 as being canceled (see claims from 2-27-04).

Claims 17-19 and 24 remain under consideration in the instant office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's arguments filed 10-8-04 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 101

Claims 17-19 and 24 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility.

Claims 17-19 are directed toward a transgenic animal having a homozygous disruption of an LRP5 gene exhibiting retinal degeneration, increased anxiety or hypoactivity.

> REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS repeated from http://www.uspto.gov/web/menu/utility.pdf

"Specific Utility" - A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material, which has a stated correlation to a predisposition to the onset of a particular disease condition, would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

(Page 5-7 of utility guidelines).

A "well-known utility" is a specific, substantial and credible utility which is well know, immediately apparent, or implied by the specification's disclosure of the properties of the material, alone or taken with the knowledge of one skilled in the art. Neither a "well-established utility" nor a "specific utility" applies to any utility that one can dream up for an invention or a utility that would apply to virtually every member of a general class of materials, such as proteins or DNA.

(Paragraph bridging pg 32-33 of utility guidelines).

The specification teaches making LRP5 -/- mice (pg 50). The specification suggests using the mice to test compounds for neurological, neuropsychological or psychotic disease, but the specification does not disclose one specific neurological, neuropsychological or psychotic disease in humans linked to a disruption in LRP5 (pg 19, lines 8-11). The mice were tested in "open field testing" (Fig. 4 and 5 and pg 51); however, the results of the open field test do not correlate to a useful phenotype because "possible increased anxiety" and "significant hypoactivity" (lines 4 and 7 of pg 51) are not specific to any disease and are not statistically significant because the number of mice tested is not disclosed and the difference observed is not significant. In fact, it cannot be determined what the "2,1," means in "2,1, -/-, Male" or "2,1, +/+, Male" in Fig. 4 and 5. The mice also had retinal degeneration. The specification suggests using the mice as a model of disease relating to disruptions in LRP5 (pg 19, lines 4-6). However, retinal degeneration has not been linked to the LRP5 gene in humans. The mice claimed cannot be used to determine compounds that modulate LRP5 expression because LRP5 is not expressed in the mice. Using the mice to determining whether a particular phenotype is ameliorated is not a specific or substantial utility because the specification does not link the phenotype to any specific disease or to a disease caused by a disruption in humans. The specification does not identify any compounds that alter neurological, neuropsychological, or psychotic phenotypes using the mice. Thus, the specification does not provide a specific or substantial use for a mouse having retinal degeneration, increased anxiety or hypoactivity as claimed.

Since the time of filing, LPR5 disruptions have been linked to osteoporosis-pseudoglioma syndrome (OPPG) in humans (Gong of record, 11-16-01, Cell, Vol. 107, pg 513-523, abstract), which is not taught or suggested in the instant application. A mouse having a homozygous disruption in LRP5 having features of osteoporosis-pseudoglioma syndrome has been made since the time of filing (Kato, of record, J. Cell Biology, 2002, Vol.1 57, pg 303-314; abstract and pg 304, col. 2, "Generation of Lrp5-/- mice"), which is not taught or suggested in the instant application.

Claim 24 is included because it is directed toward making the mouse, which lacks utility for reasons above.

Applicants argue knockout mice had a "well-known utility," i.e. "for further study of these disorders and their association with the lipoprotein-related protein 5 gene." Applicants cite MPEP 2701 II(A)(3). Applicants' arguments are not persuasive because applicants have ignored the final phrase of MPEP 2701 II(A)(3), which require a "well-established utility" must be a utility that is specific, substantial and credible.

It was well known that knockout mice could be used for scientific research to determine the function of a gene. However, scientific research is not the same as "patentable utility" or a "well-established" utility.

The MPEP and utility guidelines clearly set forth that a "well-established utility" must be specific, substantial and credible. While knockout mice were used for scientific research in the art at the time of filing, significant further research was required to determine the function of the gene. In fact, the function of the gene may never be determined from the knockout mouse. A mouse

requiring significant further research to determine the function of the gene does not rise to the level of having a "well-established utility." Using the mouse for further research is not a substantial utility, which is specifically described in the utility guidelines:

> [T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

In this case, further study of mice would have been required to determine how to use the mouse of applicants' invention to determine the function of the gene as a model of disease. The overall phenotype of the applicants' mice does not correlate to any disorder. Nor does the "expression analysis" reveal the function of the gene. Therefore, further study would be required to determine the function of the lipoprotein-related protein 5 gene or how to use the mice as a model for any disease. As such, using the mice claimed to determine the function of the lipoprotein-related protein 5 or to study "expression analysis of the lipoprotein-related protein 5 gene" is not a "substantial utility."

Using the mice to identify the function of the knocked out gene is not a "substantial utility" or "specific utility." Olsen (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and

others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway" (pg 82, last 11 lines of col. 1). Thus, knockout mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. Using mice to obtain a clue to a pathway is not a "substantial utility." Using a mouse with a phenotype caused by genes compensating for a knocked out gene is not a "specific utility" because the phenotype is not specific to the knocked out gene.

Using the mice to identify agents capable of altering a phenotype would require further research and is not a "substantial utility" or "specific utility." Bowery (Pharm. Rev., 2002, Vol. 54, pg 247-264) taught, "no unique pharmacological or functional properties have been assigned to either subunit or the variants" of $GABA_B$. "The emergence of high-affinity antagonists for $GABA_B$ receptors has enabled a synaptic role to be established. However, than antagonists have generally failed to establish the existence of pharmacologically distinct receptor types within the $GABA_B$ receptor class. The advent of $GABA_{B1}$ knockout mice has also failed to provide support for multiple receptor types" (pg 247, col. 2, lines 4-). Thus, knockout mice may be used to identify agents that bind to the knocked out gene ($GABA_B$ in the case of Bowery or lipoprotein-related protein 5 in the instant application), but the agent may not treat disease or ameliorate any symptom of disease. Further research would be required to

determine how to use such an agent identified using the mouse, which is not a "substantial utility" (see Utility Guidelines for examples of things that do not have "substantial utility" "C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility"). Using the mice to identify agents capable of altering a phenotype is also not a "specific utility" because the agent may be affecting other proteins in the pathway and not lipoprotein-related protein 5 itself. Using the mice to identify agents capable of altering a phenotype is also not a "specific utility" because the agent may be found using wild-type mice.

Overall, the mice claimed do not have a "well-established utility" because using the mice for further research (to determine how to use the mouse as a model of non-disclosed disease, to determine the function of the gene or to identify agents capable of altering a phenotype) is not a "specific utility" or "substantial utility."

Applicants cite En re Brana and conclude that the mice have utility for studying whether a disruption in LRP5 is linked to retinal degeneration in humans and for developing treatment strategies for treating patients with such a disruption. Likewise, applicants conclude the mice can be used to determine if patients with anxiety have a disruption in LRP5 and can be used to develop treatments for such patients. Applicants' argument is not persuasive. In this case, the mouse claimed does not correlate to the compounds at issue in En re Brana. The mouse may never correlate to humans with retinal degeneration or anxiety or hypoactivity because the phenotype may

be a result of other genes compensating for the disruption of LRP5, i.e. the disruption of the gene does not necessarily correlate the phenotype. Agents that treat retinal degeneration or anxiety or hypoactivity found using the mice claimed are not necessarily relevant to the disruption of LRP5 because the agents may be acting on proteins related to the LRP5 gene in a pathway and because the agents may not have any therapeutic effect.

Applicants cite Mombereau (Neuropsychopharmacology, 2004, Vol. 29, pg 1050-1062) who administered antagonists of $GABA_B$ receptor to $GABA_B$ -/- knockout mice, which caused decreased anxiety in various tests. Applicants conclude that knockout mice can be used to identify compounds that anxiety. Applicants' argument is not persuasive. First, the antagonists were not found using the mice; they were found using *in vitro* assays (see pg 1058, col. 2, 1st full ¶, lines 4-8, and Urwyler *et al,* 2003, referred to therein). Second, Mombereau concludes "we acknowledge both the inherent difficulties and the caution needed in the interpretation of behavioral analysis of genetically modified mice such as the $GABA_B(1)$ -/- mice, which have overt behavioral disturbances, in more defined tests relevant to psychopathology. Nonetheless, the current data show that even such mice can still be utilized to give important indicators of the role of a given protein, in this case the $GABA_B$ receptor, in a molecular pathway relevant for the manifestation of anxiety or depression. These assertions can then be confirmed more parametrically using appropriate pharmacological activators and antagonists as we have done using novel $GABA_B$ receptor positive modulators and antagonists" (¶ bridging pg 1059-1060). Mombereau used the antagonists to confirm

the "antidepressant-like phenotype of $GABA_B$ -/- mice pharmacologically (pg 1059, col. 1, 2nd full ¶, line 1-4). Using the mouse to obtain clues of the role of the $GABA_B$ receptor in a molecular pathway of anxiety or to confirm the phenotype of the mouse pharmacologically as described by Mombereau is not a specific or substantial utility because it is generic to a pathway of anxiety and because it does not result in determining the function of $GABA_B$ in the pathway. Too much further research would be required to determine whether "positive modulators" or "antagonists" that bind $GABA_B$ will to treat anxiety or how to modify the compounds so that they can treat anxiety.

Applicants argue the mouse is a model for osteoporosis-pseudioglioma syndrome. Therefore, applicants conclude the mouse has utility. Applicants' argument is not persuasive. The specification as originally filed did not assert the mice had utility as a model for OPPG as suggested by Gong, of record (11-16-01, Cell, Vol. 107, pg 513-523, abstract). Such a utility was not "well-established" because Gong was not available at the time of filing.

Claim Rejections - 35 USC § 112

Claims 17-19 and 24 remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use mice having retinal degeneration, increased anxiety or hypoactivity.

In addition, claims 17 and 24 do not provide a nexus between the disruption in LRP5 and the lack of production of LRP5 or the phenotypes of retinal degeneration, increased anxiety or hypoactivity.

Applicants' arguments are addressed above in the utility rejection.

Claims 17-19 and 24 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 17 and 24 remain rejected for reasons of record because it cannot be found where a mouse having a disruption in LRP5 also has hypoactivity (claims 17 and 24). Applicants have not addressed this issue.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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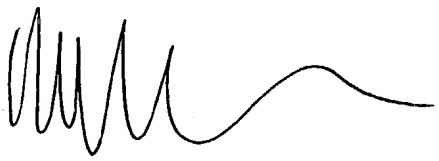
If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER